REMARKS

Claims 14, 16, 17, 20, 22, and 24 are currently pending in this application. Claims 1-13, 15, 18, 19, 21, and 23 were previously canceled without prejudice or disclaimer. Applicant requests entry of this Response to the Final Office Action and reconsideration of this application in view of the following remarks.

I. WITHDRAWN OBJECTIONS

Applicant acknowledges, with appreciation, that the Office has withdrawn the objections to the specification outlined on page 2 of the Office Action mailed February 19, 2009.

II. REJECTION UNDER 35 U.S.C.§ 103(a)

The Office maintains the rejection of claims 14, 16, 17, 20, 22, and 24 under 35 U.S.C. § 103(a) as allegedly obvious over WO 98/51333 to Deisher et al. ("*Deisher*") in view of US 2003/0228371 to Skinner et al. ("*Skinner*"), and Dardik R. et al., "Novel Proangiogenic Effect of Factor XIII Associated With Suppression of Thrombospondin 1 Expression," Arterioscler. Thromb. Vasc. Biol., 23:1472-77 (2003) ("*Dardik*"). (Office Action at pp. 3-8.) The Office cites *Deisher* for allegedly teaching "administration of many variations of the Factor XIII complex" in methods "for reducing ischemic reperfusion injury, reduction in tissue damage, vascular injury, myocardial infraction or stroke in a patient." (*Id.* at p. 3.) The Office cites *Skinner* for allegedly teaching "the use of molecules related to Factor XIIIa" in methods "designed to reduce the effects of ischemic events, such as infarctions caused by reperfusion and/or oxygen deprivation." (*Id.* at pp. 4 and 5.) The Office cites *Dardik* for allegedly teaching "that factor XIII participates in ... processes that involve angiogenesis ...." (*Id.* at p. 6.) The Office

concludes that the invention of claims 14, 16, 17, 20, 22, and 24 is allegedly obvious because "it was known that various components of the fibrinogen cascade could function to stimulate perfusion of ischemic tissues and stimulate new blood vessels." (*Id.* at p. 6.) Applicant respectfully disagrees.

Several basic factual inquiries must be made to determine whether the claims of a patent application are obvious under 35 U.S.C. § 103. These factual inquiries, set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966), require the Examiner to:

(1) Determine the scope and content of the prior art;

(2) Ascertain the differences between the prior art and the claims in issue;

(3) Resolve the level of ordinary skill in the pertinent art; and

(4) Evaluate evidence of secondary considerations.

The obviousness or non-obviousness of the claimed invention is then evaluated in view of the results of these inquiries. *Graham*, 383 U.S. at 17-18; *see also KSR Int'l Co. v. Teleflex, Inc.*, 127 S. Ct. 1727, 1734 (2007). "To reach a proper determination under 35 U.S.C. § 103, the Examiner must step backward in time and into the shoes worn by the hypothetical 'person of ordinary skill in the art' when the invention was unknown and just before it was made." M.P.E.P. § 2142, 8th Ed., July 2008 Rev. Once the findings of fact are articulated, the Office "must then make a determination whether the claimed invention 'as a whole' would have been obvious at the time to that person." *Id.*

Applicant respectfully submits that the Office has failed to establish a *prima facie* case of obviousness because the Office has relied on entirely different and unrelated prior art, and because the combination of references cited by the Office does not teach or suggest the claimed invention as a whole.

A. *Deisher* and *Skinner* are Entirely Different and Unrelated Prior Art

The Office contends that the "ischemic reperfusion injury" discussed in *Deisher* and *Skinner* "addresses all diseases which are associated with disturbed blood flow and thus include instant claims that refer to stimulating the perfusion of ischemic tissues." (Office Action at p. 3.) Applicant respectfully disagrees and again submits that *Deisher* and *Skinner*'s methods for preventing reperfusion injury involve entirely different biological phenomenon that are unrelated to the claimed methods of "stimulating the perfusion of ischemic tissues by inducing the proliferation of new blood vessels." (Claim 14.) Accordingly, one skilled in the art would not rely on the teachings of *Deisher* and *Skinner* to arrive at the instant invention.

"Ischemic reperfusion injury," as discussed in *Deisher* and *Skinner*, is a well-defined medical condition that arises if, after a certain period of ischemia, an organ is reperfused by circulating blood. Reperfusion injury is mediated by an inflammatory response in the affected tissue. For example, *Diepenhorst* teaches:

> Tissue ischemia is a key event in clinical conditions such as myocardial infarction and stroke, and may occur as a complication in vascular surgery and organ transplantation. The most evident treatment for this condition is the restoration of interrupted blood flow to the jeopardized tissue. However, reperfusion of ischemic tissue paradoxically exacerbates tissue damage, particularly after longer periods of ischemia. This negative effect of reperfusion is the result of an inflammatory reaction induced by the restoration of blood flow and is called ischemia-reperfusion (I/R) injury.
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> ...
>
> Interruption of blood flow by occlusion of afferent blood vessels and subsequent reperfusion initiates an inflammatory response and subsequent reperfusion initiates an inflammatory response in the jeopardized tissue. Within minutes of reperfusion, reactive oxygen species are

> generated, stimulating the release of cytokines and expression of adhesion molecules on damaged cells in reperfused tissues. Several hours after the onset of reperfusion, neutrophils and other inflammatory cells are activated and adhere to damaged cell membranes, further enhancing the inflammatory response. This inflammatory response ultimately leads to cell damage.

(*Id.* at p. 889 (emphasis added).)

In contrast, the instant invention relates to "stimulating the perfusion of ischemic tissues" (claim 14), which involves the formation of new blood vessels, often called "angiogenesis," in the ischemic area to improve the blood supply to the tissue. For example, *Pandya* teaches:

> Angiogenesis is the formation of new capillary blood vessels from existent micro vessels and also involves differential recruitment of associated supporting cells to different segments of the vasculature.
>
> ...
>
> The discovery of candidate molecules able to stimulate myocardial angiogenesis has stirred a growing interest in using these molecules for therapeutic application. Preliminary clinical experiences suggest that therapeutic angiogenesis may provide additional blood flow to incompletely revascularized areas.
>
> ...
>
> [A]ngiogenic growth factor therapy offers new therapeutic alternatives for patients with advanced ischemic heart disease.

(*Id.* at pp. 266, 267, and 268.) Furthermore, the specification teaches that blood vessel formation is observed 48 hours after injection of activated factor XIII (FXIIIa), a rich network of blood vessels is observed after 72 hours, and development of the vascular network continues until 96 hours after injection. (Specification at p. 4, ll. 22-27.)

As illustrated above, the instant invention relates to methods for improving the blood supply in ischemic tissue by stimulating the formation of new blood vessels over the course of several days, whereas *Deisher* and *Skinner* describe methods for preventing injury from an inflammatory reaction that occurs within minutes of reperfusion. Thus, although *Deisher* and *Skinner*'s method of preventing reperfusion injury may sound similar to the claimed methods of stimulating perfusion (since both methods use the term "perfusion"), these methods actually involve entirely different and unrelated biological phenomenon. Accordingly, one skilled in the art would not turn to the teachings of *Deisher* and *Skinner* to arrive at the invention of the currently pending claims.

Moreover, *Skinner* is also unrelated prior art because that reference describes the use of Fibrinogen A (FPA), a molecule that has nothing in common with the FXIIIa molecule recited in the currently pending claims. The Office contends that *Skinner*'s FPA molecule is "related to Factor XIIIa." (Office Action at p. 4.) Applicant disagrees. FPA is a peptide that is cleaved from fibrinogen during its conversion into fibrin by thrombin (FIIa). Thus, the resulting fibrin molecule is free of FPA. The free fibrin molecule is then a substrate for FXIIIa, which catalyzes a transglutaminase reaction in the α-chain of the fibrin molecule. In fact, *Skinner* teaches that FPA and Factor XIII play different roles in the fibrinogen cascade. (*Id.* at [0129]-[0133].) Thus, one skilled in the art would not turn to the teachings of *Skinner* to arrive at the instant invention.

Since *Deisher* and *Skinner* involve entirely different biological phenomena that are unrelated to the claimed invention, and since *Skinner* involves an entirely different molecule than the FXIIIa recited in the claims, one would not have had any reasonable expectation of success in arriving at the claimed invention based on the teachings of

those references. Accordingly, Applicant submits that the Office's reliance on *Deisher* and *Skinner* is improper for establishing a *prima facie* case of obviousness.

B. The Combination of *Deisher*, *Skinner*, and *Dardik* Fails to Teach or Suggest the Claimed Invention "As a Whole"

The Office's combination of *Deisher* and *Skinner* with *Dardik* fails teach or suggest the claimed invention "as a whole." (*See* M.P.E.P. § 2141.02.) Thus, the Office has not established a *prima facie* case of obviousness.

Specifically, currently pending claim 14, from which claims 16, 17, 20, 22, and 24 depend, recites:

> A method of treating ischemic tissues, comprising administering activated Factor XIII and thereby simulating the perfusion of ischemic tissues by inducing the proliferation of new blood vessels in the ischemic tissues.

In contrast, the combination of *Deisher*, *Skinner*, and *Dardik* fails to teach or suggest that activated Factor XIII "stimulat[es] the perfusion of ischemic tissues by inducing the proliferation of new blood vessels in ischemic tissues," as recited in the currently pending claims. Thus, the combination of references cited by the Office fails to teach or suggest the claimed invention as a whole.

Dardik is the only reference cited by the Office that discusses angiogenesis (*i.e.*, "the proliferation of new blood vessels" (claim 14)). *Dardik* discloses "in an in vitro model, FXIIIa significantly induces new vessel formation in a rabbit cornea" and that "[t]he proangiogenic effect of FXIIIa is associated with downregulation of thrombospondin (TSP-1) ...." (Specification at p. 2, ll. 32-22.) However, *Dardik* also reports that these observations "contradict the data reported by Dallabrida et al, who showed that FXIIIa inhibits capillary tube formation by human microvascular endothelial cells in a fibrin gel," and suggests that this discrepancy "may indicate that FXIIIa may

have variable effects on different types or sources of endothelial cells." (*Dardik* at p. 1477, 2nd col.) For example, "if the proangiogenic effect of FXIIIa is mediated at least in part by TSP-1, it is possible that cells with lower TSP-1 synthesis will be less responsive to the effect of FXIIIa." (*Id.*) Thus, based on the teachings of *Dardik*, one skilled in the art would not predict that the proangiogenic effect of FXIIIa observed in rabbit corneas would also occur in ischemic tissues, or that activated Factor XIII could be used to induce "the proliferation of new blood vessels in ischemic tissues," as recited in the currently pending claims.

Neither *Deisher* nor *Skinner* cure this deficiency in *Dardik*, since these references do not teach or suggest any role for activated Factor XIII in stimulating the proliferation of new blood vessels in ischemic tissues. *Deisher* does not discuss angiogenesis at all, and although *Skinner* makes a passing reference to "methods utilizing animal models of new vessel angiogenesis" (*Skinner* at [0082] and [0127]), *Skinner* provides no evidence to establish any connection between the methods disclosed therein and new vessel angiogenesis. The Office has failed to identify any teachings in *Deisher* or *Skinner* regarding the applicability of using activated Factor XIII to induce angiogenesis in ischemic tissues. Instead, the excerpted portion of *Skinner* on pages 7-8 of the Office Action teaches that "[t]reatment of ischemia typically involves reduction of blockage" (Office Action at p. 5 (citing *Skinner* at [0196])), which is completely different from "inducing the proliferation of new blood vessels in ischemic tissues," as recited in the currently pending claims.

The Office appears to suggest that anti-infarction activity includes the proliferation of new blood vessels and, therefore, *Deisher* and *Skinner* allegedly teach "inducing the proliferation of new blood vessels in ischemic tissue." (*See* Office Action

at p. 6 ("anti-infarction, i.e., increased perfusion and increased blood vessel formation, activity.").) Applicant disagrees. As discussed above, *Deisher* and *Skinner*'s methods of preventing reperfusion injury are entirely different and unrelated to the instantly claimed method of promoting angiogenesis. In fact, *Deisher* does not discuss angiogenesis at all and *Skinner* fails to establish any nexus between anti-infarction molecules and new vessel angiogenesis. *Dardik* fails to cure these deficiencies in *Deisher* and *Skinner*, because *Dardik* does not address angiogenesis in ischemic tissues. Since, the Office has failed to provide any articulated reasoning having some rational underpinning for the conclusion that anti-infarction activity includes the proliferation of new blood vessels, the Office cannot establish a *prima facie* case of obviousness.

The Office also appears to suggest that the induction of new blood vessels in ischemic tissue is an inherent property of administering activated Factor XIII. (*See* Office Action at p. 8 (stating *Deisher* contemplates "a method of treating ischemic tissues comprising administering activated Factor XIII, which would naturally thereby stimulate the induction of new blood vessels.").) In response, Applicant respectfully reminds the Office that "[o]bviousness cannot be predicated on what is not known at the time an invention is made, even if the inherency of a certain feature is later established." M.P.E.P. § 2141.02, citing *In re Rijckaert*, 9 F.2d 1531 (Fed. Cir. 1993). The Federal Circuit and its predecessor court have long noted that "inherency is quite immaterial if ... one of ordinary skill in the art would not appreciate or recognize that inherent result." *In re Naylor*, 152 U.S.P.Q. 106, 108 (C.C.P.A. 1966). Moreover, "[t]hat which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown." *Rijckaert*, 9 F.2d at 1534. Thus, in order for an invention to be obvious, one

of ordinary skill in the art, at the relevant time period, must necessarily have been aware that the particular combination of references would produce a method having all of the limitations of the claimed invention. That is not the case here.

As discussed above, *Dardik* expressed significant doubt regarding whether activated Factor XIII would exhibit proangiogenic properties in tissues other than rabbit cornea. (*See Dardik* at p. 1477, 2nd col.) *Deisher* and *Skinner* fail to dispel those doubts, because *Deisher* does not discuss angiogenesis, and *Skinner* fails to establish any nexus between the methods disclosed therein and new vessel angiogenesis. Since obviousness cannot be predicated on what is unknown, the Office has failed to establish a *prima facie* case of obviousness because the combination of references fails to teach or suggest the claimed invention as a whole.

C. Conclusion

Applicant has demonstrated for the first time that activated Factor XIII stimulates the perfusion of ischemic tissues by inducing the proliferation of new blood vessels. (*See* Example 3.) These unexpected results are recited in the currently pending claims. When a patent application claims an invention that works in an unexpected and fruitful manner, the invention is non-obvious. *See KSR*, 127 S. Ct. at 1740 (2007).

For at least these reasons, Applicant submits that the Office has failed to establish a *prima facie* case of obviousness because the combination of *Deisher*, *Skinner*, and *Dardik* fails to teach or suggest that activated Factor XIII "stimulat[es] the perfusion of ischemic tissues by inducing the proliferation of new blood vessels," as recited in the currently pending claims. Accordingly, Applicant respectfully requests that the Office withdrawn this rejection under 35 U.S.C. § 103(a).

III. CLOSING

Applicant respectfully requests that the Office enter this Response under 37 C.F.R. § 1.116, placing claims 14, 16, 17, 20, 22, and 24 in condition for allowance. Since this Response does not present any claim amendments, it should allow for immediate action by the Examiner.

Furthermore, Applicant respectfully points out that the Final Office Action presented some new arguments as to the application of the art against Applicant's invention. It is respectfully submitted that entering this Response will allow Applicant to reply to the final rejections and place the application in condition for allowance.

Finally, Applicant submits that entering this Response will place the application in better form for appeal, should the Examiner continue to dispute the patentability of the pending claims.

In view of the foregoing remarks, Applicant submits that this claimed invention is not obvious in view of the prior art references cited against this application. Applicant therefore requests the entry of this Response, the Examiner's reconsideration of the application, and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to Deposit Account No. 06-0916.

Respectfully submitted,

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Dated: April 1, 2010

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Attachments:

- Diepenhorst G.M.P. et al., "Complement-Mediated Ischemia-Reperfusion Injury: Lessons Learned from Animal and Clinical Studies," Annals of Surgery, 249:889-899 (2009) ("*Diepenhorst*"); and
- Pandya N.M. et al., "Angiogenesis - a New Target for Future Therapy," Vascular Pharmacology, 44:265-74 (2006) ("*Pandya*").